Current Sexual Health Reports
https://doi.org/10.1007/s11930-024-00394-1

Post-Orgasmic Illness Syndrome in Men: A Literature Review of a Challenging Condition

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Accepted: 17 July 2024
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Abstract

Purpose of Review To synthesize the current literature and contemporary landscape about promising advancements in clinical interventions targeting post-orgasmic illness syndrome (POIS).

Recent Findings PubMed search was performed, and articles were screened for relevance. 24 articles were deemed suitable for inclusion. Various pathophysiological mechanisms for POIS have been proposed, including immunologic hypersensitivity and sympathetic dysregulation. This syndrome may manifest post-intercourse, post-masturbation, or following spontaneous ejaculations, with flu-like symptoms persisting for a span of up to 7 days.

Summary Recurrent presentations of these symptoms significantly deteriorate both quality of life and sexual function in patients diagnosed with POIS, often leading to cognitive impairment and mood disturbances. While various therapeutic modalities have demonstrated efficacy in providing short-term relief, the management of acute episodes remains contentious. Furthermore, the dearth of longitudinal data hampers the establishment of definitive long-term management strategies for POIS sufferers.

Keywords Post-orgasmic illness syndrome · Ejaculation · Flu-like symptoms · Diagnostic criteria · Hyposensitization · Sexual dysfunction

Introduction

Post-orgasmic illness syndrome (POIS) is an infrequent array of symptoms following ejaculation, initially delineated by Waldinger and Schweitzer in 2002 [1]. Their study reported patients complaining of flu-like manifestations, encompassing myalgias, fatigue, and pronounced warmth, alongside localized allergic presentations like sore throat, postnasal drip, skin reddening, and ocular burning sensations, manifesting shortly post-ejaculation. These symptoms emerged rapidly within seconds to hours post-ejaculation, followed by cognitive impairment, including reduced concentration and irritability [2].

Typically, POIS symptoms arise post-intercourse, masturbation, or nocturnal emissions, persisting for 3 to 7 days. To mitigate symptomatology, individuals with POIS often curtail sexual activity or abstain altogether [1, 3, 4]. The consequences of POIS, both physical and psychological, significantly impinge upon patients' quality of life.

Due to scant research, the prevalence and incidence of POIS remain obscure, with fewer than 100 documented cases since its inception [5, 6]. Acknowledged as a rare disorder by the National Institutes of Health Office of Rare Disease Research, POIS has garnered increasing attention through self-reported cases on internet platforms, hinting at underdiagnosis and underreporting [7]. As understanding of POIS symptomatology matures, more patients are anticipated to pursue evaluation and treatment, potentially alleviating misdiagnoses of psychiatric or somatic symptom disorders. This review aims to furnish an updated synthesis

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Published online: 25 July 2024

of POIS literature, exploring its pathophysiology and potential management strategies.

Methods

Type of Study

The research is characterized as a cross-sectional, exploratory, evaluative study, comprised of a survey of studies addressing Post-Orgasmic Illness Syndrome. It is an integrative literature review study that encompasses various methodologies, providing a comprehensive analysis of the literature, promoting better performance in evidence-based pharmaceutical care practices.

The methodological framework followed was developed in five stages: 1- Identification of the theme and formulation of the research question; 2- Establishment of eligibility criteria and literature search; 3- Selection and reading of titles and abstracts of publications; 4- Exclusion of publications that do not meet the inclusion and exclusion criteria and others lacking consistent information; 5- Inclusion of publications that met the research criteria and addressed the guiding question based on databases.

Inclusion and Exclusion Criteria

The online database of the US National Institute of Health (PubMed) was used, utilizing the following descriptors according to the structured vocabulary of the health sciences descriptors (DeCS). The search was conducted in April 2024, using inclusion criteria such as the presence of the descriptors "Post-Orgasmic Illness Syndrome," "Diagnosis and Clinical Management," "Etiology." Because of the paucity of studies, our search was ampliated to articles published between 2000 and 2024 in Portuguese or English languages. Exclusion criteria included incomplete articles, those published in languages other than those chosen for inclusion criteria, and those published prior to 2000. Corresponding English versions were also sought. For the search of scientific publications, the descriptors were crossed with the term "AND."

Summary of Evidence

The data analysis procedures were carried out as follows: initial screening involved reading the titles, followed by reviewing the abstracts. Subsequently, selected articles underwent full-text reading, leading to the final sample.

Pathophysiology

The pathophysiology of POIS has yet to be thoroughly elucidated, with various hypotheses proposed to explain it, including immunological phenomena, opioid-like withdrawal, neuroendocrine responses, transient autonomic nervous system deregulation, hypersensitivity, and disordered cytokines [1, 2, 8, 9].

Waldinger et al. propose a predominant theory, suggesting an autoimmune or allergic reaction to a component of semen as the underlying cause. This theory is linked to an immunomodulated Type I (immediate type, involving antigen cross-linking with membrane-bound IgE antibody of mast cells or basophils) and Type IV (delayed type, cell-mediated response involving T-cells, monocytes, and macrophages) allergy to semen by the mucosa of the urethra [9]. Their study involving 45 POIS patients supported this hypothesis, as indicated by positive skin prick test (SPT) results [4].

In the attempt to find a probable cause, Waldinger observed the occurrence of POIS both before and after sterilization in three men. This finding suggests that the antigen (Ag) that triggers the immune response is likely not attached to the sperm cells but rather associated with the seminal fluid. Following sterilization, spermatozoa are no longer released into the reproductive system, but seminal fluid production continues, originating from organs like the prostate and/or seminal vesicles [2].

Jiang et al. conducted skin testing with autologous semen on a Chinese man displaying allergic rhinitis and POIS symptoms, comparing the results with those of three healthy individuals. Their findings suggested that IgE-mediated semen allergy may not fully explain POIS symptomatology. Instead, they proposed that chemical imbalances in the brain could underlie POIS, linking its symptoms to opioid withdrawal. They hypothesized that the orgasmic process depletes endogenous opioids, potentially activating endogenous μ-opioid receptors and leading to symptoms resembling opioid withdrawal [5].

Conversely, some authors suggest that an IgE-mediated mechanism is less probable, proposing instead that chemical imbalances in the brain, along with psychological factors, may underlie POIS, serving as potential risk factors [10].

Several studies have reported an association between ejaculatory disorders during sexual intercourse and decreased serum testosterone levels. Bolanos and Morgentaler, as well as Takeshima et al., suggested testosterone deficiency related to hypogonadism as a possible cause. This deficiency was treated with human chorionic gonadotropin (hCG) or testosterone therapy [11, 12].

Clinical Presentation

The symptoms typically resemble those of the flu but may progress to cognitive impairment, lasting from 1 to 7 days, with spontaneous resolution. They may recur with each new ejaculation, regardless of age, and can manifest after the first ejaculation [1, 13]. The most commonly reported manifestations were fatigue (68.7%), poor concentration (63.9%), irritation (51.9%), fever (50.4%), headache (44.2%), nasal congestion (37.8%), myalgia (35.8%), itchy eyes (33.5%), and throat symptoms (16.8%) [13]. Waldinger et al. defined POIS as primary, when it manifests in young patients in the beginning of sexual life (49%) and secondary, when starts after a period of ejaculation without symptoms (51%) [4]. Similarly to Waldinger's classic symptoms description of POIS, Peters et al. reported a case of a male complaining of coughing, rhinorrhea, sneezing, as well as a hive-like rash on his forearms after ejaculation. In addition to what was seen in most of POIS cases, he also noticed facial and cervical lymphadenopathy which worsened with increased frequency of ejaculation [14].

POIS in women can mimic other conditions, such as sexually transmitted infections, hormonal disorders, and psychological problems, making accurate identification difficult. Waldinger [2] hypothesizes that POIS in women is related to female prostatic tissue located around the vagina, which could generate specific antigens. However, the lack of specific diagnostic criteria for POIS in women makes diagnosing the condition challenging. Most studies on POIS focus on men, this means that there is still significant lack of data about the characteristics, causes, and treatment of POIS in women.

Diagnosis

The Five Preliminary Criteria

Based on an observational study of 12 Dutch males, POIS was categorized POIS using five preliminary criteria. Subsequently, these criteria underwent assessment in a cohort of 45 males whose symptoms closely corresponded to the majority of the outlined criteria [4]. Although a variation of symptoms was noticed among patients, POIS presentations were adequately represented by these criteria. The five criteria of POIS are listed below:

I. *Criterium 1*. One or more of the following symptoms: Symptoms encompass flu-like sensations, extreme fatigue, muscle weakness, feverishness, mood disturbances, memory difficulties, concentration problems, incoherent speech, nasal congestion, runny nose, and itchy eyes.
II. *Criterium 2*. All symptoms manifest promptly, within seconds, minutes, or hours post-ejaculation, whether induced by sexual intercourse, masturbation, or spontaneous nocturnal emissions.
III. *Criterium 3*. Symptoms exhibit persistence, occurring consistently or nearly always, impacting over 90% of ejaculation instances.
IV. *Criterium 4*. Most of these symptoms endure for about 2 to 7 days post-ejaculation;
V. *Criterium 5*. Symptoms spontaneously resolve without necessitating specific intervention.

The Seven Clusters of Waldinger's Diagnostic Criteria

As an addition to the clinical criterion, Waldinger et al. also suggested dividing the symptoms from Criteria 1 into seven different clusters based on the patients' own words, and categorized in general, flu-like, head, eyes, nose, throat and muscle, as follows: [4]

I. *Cluster 1 (general cluster)*: Extreme fatigue, exhausted, palpitations, problems finding words, incoherent speech, dysarthria, concentration difficulties, quickly irritated, cannot stand noise, photophobia, depressed mood;
II. *Cluster 2 (flu-like cluster)*: Feverish, extreme warmth, perspiration, shivery, ill with flu, feeling sick, feeling cold;
III. *Cluster 3 (head cluster)*: Headache, foggy feeling in the head, heavy feeling in the head;
IV. *Cluster 4 (eyes cluster)*: Burning, red injected eyes, blurred vision, watery, irritating, itching eyes, painful eyes;
V. *Cluster 5 (nose cluster)*: Congestion nose, watery, runny nose, sneezing;
VI. *Cluster 6 (throat cluster)*: Dirty taste in mouth, dry mouth, sore throat, tickling cough, hoarse voice;
VII. *Cluster 7 (muscle cluster)*: muscle tension in back or neck, muscle weakness, pain muscles, heavy legs, stiffness muscles.

Diagnostic Tests and Differential Diagnosis

Due to the unclear pathophysiology of POIS, diagnosing it can be quite challenging and often involves ruling out other potential causes. Conditions such as benign orgasmic cephalgia, orgasmolepsy, upper respiratory tract

infections and allergic rhinitis may present with symptoms similar to those described by Waldinger et al [4]. Apart from conducting a detailed history and physical examination, standard diagnostic tests are recommended, including complete blood work, including serum electrolyte levels, kidney and liver function tests, and assessment of sex hormone levels, as well as urine studies [8]. SPT is commonly used for diagnosis, but further studies are required to prove it's utility. Some studies have explored the association between serum total IgE levels and POIS incidence. Additional diagnostic modalities, such as The International Index of Erectile Function scale, brain/vessel imaging, and cystoscopy, have been employed to rule out alternative diagnoses, but their clinical efficacy in the context of POIS warrants further investigation [7, 15–17].

Discussion

POIS is a rarely diagnosed condition, and a single most effective therapy is not yet known. There have been many attempts to validate the criteria for the diagnosis of POIS, like a recent study with over 100 patients, which 97% of then, who were diagnosed with POIS, fulfilled at least three or more criteria with approximately 40% fulfilling all 5 criteria. However nearly 40% of the patients did not present these symptoms with every episode of ejaculation. For this reason, Strashny et al. [18] proposed an amendment to criterion 3 adjusting through the presence of symptoms in being greater than 90% of the ejaculation episodes.

Based on a theory of chemical imbalance in the central nervous system triggered by psychological factors, Depreux et al. [10] showed that the use of benzodiazepines and selective serotonin reuptake inhibitors partially alleviated psychological symptoms without affecting somatic changes. To address ejaculation frequency, flutamide, an androgen receptor antagonist, was administered [1]. This led to reductions in both spontaneous ejaculations and intercourse frequency, while somatic and psychological symptoms remained unaffected.

Since some studies suggests that the pathophysiology is related to allergy/immunomodulated phenomena, Waldinger et al. attempted desensitization by injecting patients with diluted autologous semen, progressively increasing the concentration based on clinical response. They reported one patient experiencing 60% symptomatic improvement over 31 months with an improvement in premature ejaculation, while another patient experienced 90% symptomatic improvement over 15 months. However, this treatment option is costly, requires frequent office visits for injections, and many providers may not be experienced or comfortable with injecting semen [4, 9].

McLean-Tooke et proposed another alternative for the therapy of POIS based on immune regulation. Omalizumab, an anti-IgE monoclonal antibody currently approved for the treatment of asthma and chronic urticaria, was offered for the therapy of POIS with satisfactory results [19].

De Amics et al. [16] reported a patient with POIS had positive specific IgG in vitro tests, indicating exposure, but negative specific IgE, suggesting no sensitivity to his own semen proteins. Despite this, he underwent a desensitization protocol with his semen, initially experiencing symptom improvement in the first year but ultimately discontinuing treatment after two years due to limited efficacy. He was also referred to a psychologist but only continued treatment for less than six months. Immunophenotypical analysis revealed decreased B cell and NK cell counts, with a notable increase in a subset of NK cells not typically found in healthy individuals, but it was not able to confirm the allergy IgE mediated syndrome [16]. Trying to correlate symptoms with the allergic response to semen exposure, a Chinese study compared patients diagnosed with POIS to controls. Both groups were submitted to SPT, intracutaneous tests, and specific IgE detection. Both patients and healthy controls had positive intracutaneous test results with their own semen, negative SPT results, and no IgE specific to autologous semen. Besides, most patients (4/5) did not achieve ideal therapeutic effects with desensitization. These results confront previous studies that correlated allergic response and POIS [20]. Interestingly, POIS symptoms do not manifest during the storage of semen in the seminal vesicles but only during ejaculation. It remains unclear whether the immune response to seminal fluid is specifically related to the urethral mucosa, which could explain why symptoms are triggered during the emission of seminal fluid.

Bolanos and Morgentaler et al. [11] diagnosed one patient with POIS associated with testosterone deficiency. Due to desire for fertility, the testosterone deficiency was treated with hCG 1500u three times weekly to avoid possible infertility and testicular volume reduction related to the use of exogenous testosterone. The patient presented with improvement in serum testosterone levels, reduction of weakness, anxiety and brain fogging. After 6 months, the patient showed increase in ejaculation frequency and mild post-orgasmic symptoms. Meanwhile, Takeshima et al. [12] diagnosed a young patient with low free testosterone levels with POIS and no desire for fertility. The patient initially received celecoxib 200 mg, an NSAID, daily post-ejaculation, which led to immediate relief of headache and muscle pain, enabling him to ejaculate three times per week. However, general fatigue persisted. Subsequently, alongside NSAIDs, the patient received testosterone therapy with

250 mg of testosterone enanthate every 2 weeks. Patients presented significant improvement in general fatigue, morning erections became consistent, allowing daily ejaculation through masturbation.

Most investigations into the physiological role of testosterone in ejaculatory disorders have primarily relied on animal models, with scant human-based studies examining the correlation between serum testosterone levels and ejaculatory function [11]. Multiple studies have indicated a link between ejaculatory disorders during sexual intercourse and reduced serum testosterone levels [21, 22]. However, only a handful of prior studies have suggested an association between testosterone and POIS [11, 12].

Peters et al. [14] reported that the most effective treatment found was daily fexofenadine, resulting in a remarkable 90% improvement in symptoms. Interestingly, the patient did not experience significant symptom relief when taking diphenhydramine, despite its similar mechanisms of action. This disparity could be attributed to diphenhydramine's short half-life and rapid peak serum concentrations within 2 h. Conversely, fexofenadine's prolonged duration of action and non-sedating nature make it more tolerable for regular use [14].

Different approaches designed to prevent patients' contact with semen. Reisman et al. [17] investigated the potential effect of on-demand silodosin, considered to cause anejaculation, as first-line therapy. Additional treatment with ibuprofen and prednisone was then administered depending on clinical response. In this study, 57% of males were effectively treated with silodosin. Patients refractory to silodosin were managed with ibuprofen (28.5%) and prednisone (80%). A more invasive approach was proposed by Huang et al. [23] Bilateral epididymectomy and vasoligation was performed in a patient with POIS refractory to immunosuppressive therapy, including prednisone and mycophenolate. The patient reported symptom resolution at 2-mo follow-up. This approach challenges the findings of Waldinger et al. [2], who reported POIS symptoms in men both pre- and post-vasectomy, suggesting that the immunological reaction was triggered by seminal fluid. A potential procedure to definitively induce anejaculation is radical prostatectomy. Consequently, this surgery could prevent any contact with seminal fluid in males with POIS. Future studies should evaluate the effects of radical prostatectomy in males with both prostate cancer and POIS. While we acknowledge that offering radical prostatectomy solely as a solution for POIS in males without prostate cancer is not advisable due to potential complications, such as urinary incontinence and erectile dysfunction. But, patients with both conditions may benefit from this surgery.

POIS has significant negative impact on couples' relationship, general and mental health and well-being. Up to 51% of men with POIS has sought medical help to treat these symptoms. For many patients, abstinence is an alternative to preclude symptoms initiation [24].

In summary, symptomatic treatment with antihistamines, such as fexofenadine, has been shown to be helpful for some patients, possibly significantly reducing symptoms related to allergic reactions [14]. Nonsteroidal anti-inflammatory drugs can help relieve muscle and joint pain [12, 17]. In specific cases, other medications, such as antidepressants and benzodiazepines, may be considered [10]. However, there is still a lack of evidence for non-drug treatment in the approach to the patient with POIS, such as individual and couples' psychotherapy, as well as other psychosexual therapies. To date, there is no evidence to support any specific therapy as the first-line treatment, as none of the aforementioned modalities are highly effective. We recommend an individualized approach for each patient, prioritizing the primary symptoms. It is reasonable to initiate therapy with medications that have fewer side effects and to increase the complexity of the treatment if initial efforts are unsuccessful.

Limitations

Research on POIS still faces several limitations that hinder a complete understanding of the condition and the development of effective solutions for patients. One of the main limitations lies in the small sample sizes in previous studies, which makes it difficult to generalize the results to the broader population. In addition, the lack of control groups in many studies prevents definitive determination of whether the observed differences in POIS patients are actually caused by the condition or by the influence of other factors, such as demographic variables or lifestyle.

To overcome these limitations, further research is needed. Studies with larger groups of POIS patients are essential to confirm the results of previous studies and identify new risk factors and clinical characteristics. The inclusion of control groups in studies is crucial to determine whether the observed differences in POIS patients are actually caused by the condition or by other factors. Mechanistic studies are needed to elucidate the pathophysiological processes underlying POIS. The search for specific biomarkers for POIS can aid in diagnosis and assessment of treatment response. Finally, randomized controlled treatment trials are essential to evaluate the efficacy of different therapeutic approaches for POIS.

Conclusions

In light of the comprehensive analysis of the scientific literature on POIS, it is evident that this clinical condition represents a significant challenge in terms of diagnosis and understanding. Nevertheless, it is crucial for urologists to possess a comprehensive understanding of its presentation and management. The paucity of available studies highlights the necessity for further research to enhance our understanding of the pathophysiological mechanisms underlying POIS. It's important to acknowledge that the treatment of this condition can be approached through a wide array of options, that needs to be individualized for each patient and each possible pathophysiology present, each with varying outcomes.

Author Contributions VFNL - researched pubmed and summarized data. wrote pathophysiology, clinical presentation and discussion. DJAVL - researched pubmed and summarized data. wrote methods and conclusion.TFNL - wrote introduction, clinical presentation, discussion, conclusion, made tables.all authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare that they have no competing interests.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Competing Interests The authors declare no competing interests.

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